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Introductory Chapter: Cognitive Disorders and Its Historical Background

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Additional information is available at the end of the chapter

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1. Introduction

Dementia is a neurodegenerative disorder characterized by a progressive decline in multiple cognitive domains leading to deterioration of daily living activities, including social and professional functioning. The aging population has been increasing gradually, and in 1990, 26 countries with more than 2 million elderly citizens aged 65 years and older were identified. It is expected that by 2013 another 34 nations will be added in the list. On the other hand, calculations made in 2000 about the number of elderly peoples (over 65 years old) in the world reached the 420 million (7%), and they estimated around 1 billion by 2030 (12%), mainly in developing countries [1].

Without doubt, the most common form of dementia in elderly people is Alzheimer disease (AD), but it can occur even in patients with 40 years of age.

AD is a progressive disorder of multifactorial origin, well defined clinically with a number of biomarkers also well documented. According to the World Alzheimer Report from 2015, AD will increase exponentially as population ages being one of the biggest problems of our society in this century [2]. Currently, 46.8 million people live with dementia all over the world, and this number will be duplicated every 20 years. Today, the calculated incidence of dementia is 9.9 million new patients, one new one every 3.2 s.

The Monzino 80+ population-based study made in 2015 found that one quarter of 80+-year-old person had dementia even in advanced stages which increased prevalence in extreme ages such as: 15.7% in persons aged 70–84 years to 52 and 65.9% in peoples aged 95–99 and in beyond 100 years, accordingly [3].

Another author reports that 24.3 million patients have dementia at the present moment, and the incidence is 4.6 new cases yearly. They said the number of patients will be duplicated every 20 years to more than 81 million (71%) by 2040 most of them in developing nations [4]. Other author highlighted that the number of patients living with dementia (PLWD) will be a triple by 2050 [5].

We also agree with Vito Moretti [6] who wrote about “Update on Dementia” that the whole society should be involved in the mental health promotion to reduce risk of dementia and in new priorities for research purposes to identify new approaches to this problem and eradicate stigma and discrimination.

The delivery of therapeutic agents specifically designed to enhance memory and cognition in AD patients is increasing gradually. The limited efficacy of the drugs currently available is well known, and the introduction of these medications has shed an entirely new light on the field. Therefore, we believe that this is the best time to look at the past to understand the present and perhaps gain insight into the future [7].

2. Ancient times

Neurological injuries, such as traumatic hemiparesis and cervical dislocation with paraplegia, were described in the well-known Edwin Smith surgical papyrus. Similarly, recognizable in the Ebers papyrus is a description of migraine, but the history of dementia is probably as old as mankind, at least since lifespan reached the age of 60 years of age. After several searches of previous record in the medical literatures in order to summarize the opinions for dementia in ancient China, the earliest description of dementia in the Yellow emperor’s internal classic it is found in a book written 2000 years ago. The term of dementia was first delivered by Hua Tuo (AD 140–208) in the book, Hua Tou Shen Yi Mi Zhuan [8].

In the above-mentioned book, the author mentioned that the insufficiency of flowing energy (Qi) is one of the causes of dementia among other such as the stagnation of phlegm; and the stasis of the blood which confirm that dementia disorders were investigated by traditional Chinese medicine in ancient times [8].

An inscription from the tomb of the vizier Westphal, dated c. 2455 BCE, seems to describe stroke, and Herodotus describes epilepsy in Hellenistic Egypt [9].

In the past, everyone presenting an incapacity for reasoning properly including psychosis, neurosyphilis, and other mental disorder was labelled as dementia. Elderly patients presenting similar clinical manifestations, were considered secondary to hardening of the brain arteries.

Dementia has been described to in medical texts since ancient times. One of the earliest known references to dementia is delivered to the 7th century BC Greek philosopher Pythagoras, who included in that concept “senium” peoples aged oldest than 63 years old (a period of mental and physical decay), and after age of 80th being where *“the scene of mortal existence closes after a great length of time that very fortunately, few of the human species arrive at, where the mind is reduced to the imbecility of the first epoch of infancy”* [10].

The Greek statesman and poet Solon established that if a male people's loss his capacity for judgment due to old age then terms of man's will might be invalidated, this happened in 550 BC and the Chinese authors considered the medical term of dementia related to "foolish old person" [11].

Two ancient Greeks Aristotle and Plato (**Figures 1 and 2**) wrote about mental decay in elderly persons and they considered that process as an inevitable one affecting all old peoples without possibility of its prevention. They also said that these kinds of person were not suitable to carry out high responsibilities or any position because this disorder affects their judgment, imagination, reasoning and memory [12].

A more advanced statement about dementia was established by Cicero who defined it as a process not inevitable related with the aging that "*affect only those old men who were weak-willed.*" Cicero also said that dementia could not happen in those persons who remained mentally active and with the capacity to learn new things. Unfortunately, the Aristotle's medical writing prevailed for several centuries above the most modern Cicero's views on aging, and other physicians such as Galen and Celsus simply highlighted the Aristotle's belief [13]. Nevertheless, other authors from Greece and Rome delivered other ideas more similar to our modern concept of dementia including many cognitive and behavioral symptoms of dementia [14].

May et al. [15] delivered the results of electronic searches of Zhong Hua Yi Dian ("Encyclopaedia of Traditional Chinese Medicine"), a CD of 1000 premodern (before 1950) medical books, for single herbs, and other natural products used for dementia, memory disorders, and memory improvement.

They found 127 different books containing 731 citations about products for treatment of memory disorders. A total of 110 natural products for the management of memory problems were identified including yuan zhi (*Polygala tenuifolia*), fu shen (*Poria cocos*), and chang pu (*Acorus spp.*) All the above-mentioned products have been cited many times in the literature over the past 180 years.

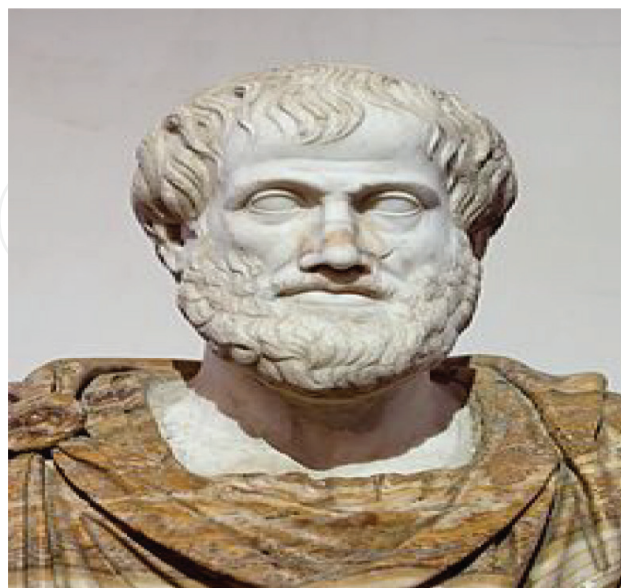


Figure 1. Roman copy in marble of a Greek bronze bust of Aristotle by Lysippos, c. 330 BC. The alabaster mantle is modern. Born 384 BC in Northern Greece. Died 322 BC in Euboea Greece (Source: <https://en.wikipedia.org/wiki/Aristotle>).

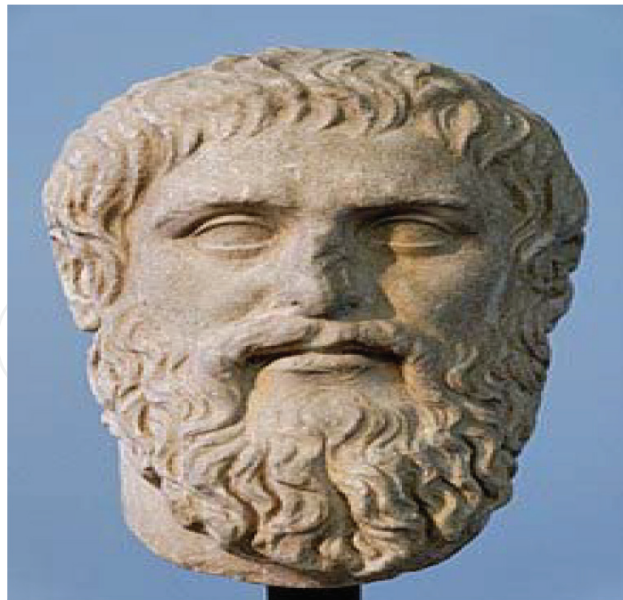


Figure 2. Plato: Roman copy of a portrait bust by Silanion for the Academia Athens. Born 428/427 or 424/423 BC in Athens, Greece. Died 348/347 BC (age) c. 80. Athens (source: <https://en.wikipedia.org/wiki/Plato>).

Dementia was defined in the ancient period (under Ayurveda) as well. The ancient period dates back to the mid-second millennium Before Christ (B.C.) during the creation of the Ayurvedic Indian system of Medicine, which detailed descriptions of neurological disorders called Vata Vyadhi. Knowledge about dementia was increasing gradually through the early twentieth century witnessed the birth of modern Indian medicine with the onset of formal physician training at the nation's first allopathic medical colleges located in Madras (1835), Calcutta (1835) and Mumbai (1848) [16].

Neurology, in the modern sense, did not exist in ancient times, where medicine was a group of belief, magical, natural, and religious elements. There were different practitioners for each form of therapy. However, Egyptian doctors made careful observations of illness and injuries, including problems of the nervous system. Egyptians had words for the skull, brain, vertebrae, spinal fluid and meninges, though they do not say if they assigned any function to them. They also described unconsciousness, quadriparesis, hemiparesis and dementia [17].

Even in contemporary societies, extended life expectancy results in elderly leaders, suffering from various diseases connected with gerontology and without exception, their peoples and the whole nation suffer the consequence. From 87 Byzantine emperors, 7 of them reached older age and showed symptoms of dementia, as well as other manifestations of elderly peoples.

Many Byzantine doctors considered dementia secondary to multiple causes mainly some kind of pathogenic humor and cerebro-vascular disorder.

Loss of mental skills is considered dangerous and remains a problem from antiquity to the modern day. Fortunately, Byzantium handled all these cases with diplomacy [18].

The reference to "imbecility" was described for the first time in Greece around sixth century BC and the Japanese term "Mow-roku" (age and devitalized) in eleventh century. In 1960, this

term was replaced by “Chee-hou” (absent-mind imbecile), and finally in 2014, it was changed by “Nonchee-show” for humanistic reasons [19].

In Constantinople, there was one special hospital to admit those patients with dementia or insanity excepting the emperors who were above the law and whose health problems could not be divulged publicly. During 1700 years, information about dementia on Western medical literature was poorly recorded.

In the thirteenth-century, Roger Bacon wrote about dementia who considered advanced ages as celestial punishment for original sin. He also delivered the same Aristotelian’s criteria saying that dementia is a natural consequence of long lifespan but established that the brain was the center of memory and not the heart [20]. Years later, poets, novelists, and other playwrighter’s mentioned the loss of mental function secondary to old age, and it should be highlighted Shakespeare and his allusion to dementia in his play Hamlet and King Lear [21, 22].

At that time, elderly people presenting dementia was called as senile dementia or senility, and it was considered as a normal consequence of the advance age and not a brain disorder, but years later, the same cause of the same problem was identified as cerebral atherosclerosis and or ischemic stroke in the cerebral vascular territory.

Before the end of nineteenth century, the concept of dementia is wider than twentieth century and later and under the umbrella of that definition, it was included several mental disorders and any type of psychosocial disability, including conditions that could be reversed [23].

The history of vascular dementia is related to patients presenting cognitive decline post apoplexy reported by Thomas Willis in 1672. In almost all eighteenth and at the beginning of nineteenth century, the pathological process of “brain congestion” was the most common diagnosis performed by the medical doctors when several conditions ranging from stroke to anxiety and to dementia due to effects of untreated hypertension were diagnosed.

The modern history of vascular dementia is written by Otto Binswanger and Alois Alzheimer (**Figure 3**). In 1894, they had a merit to distinguish vascular dementia from dementia paralytica caused by tertiary syphilis [24].

In 1907, a 50-year-old lady presenting a cognitive decline and some associate microscopy abnormalities in the brain was reported by Alois Alzheimer who considered it as a rare disorder of the middle age. Alzheimer’s findings were originally published in the form of a conference abstract where the author described a delusional woman (Auguste D) who had slowly lost her cognitive function and died at 55 years of age [25].

In recognition of the job done by Alois Alzheimer (1864–1915), Emil Kraepelin introduced the term of Alzheimer’s disease in 1910 and also differentiated the presenile form of dementia (reported by Alzheimer) from the commonest senile variant [26].

During the first half of the twentieth century, the vascular etiology for almost all cognitive disorders was prevalent until 1960s where the link between neurodegenerative diseases and age-related cognitive decline was documented. Ten years later, the vascular etiology of dementia is considered less common than was before though and AD the commonest cause of almost



Figure 3. Emil Kraepelin in his later years. Born in 1856 and died in 1926 (aged 70). (Source: https://en.wikipedia.org/wiki/Emil_Kraepelin).

all mental impairment in elderly peoples. Currently, it is well known that vascular dementia and AD can be associated.

Around 2010, many countries have 10–14% of people over 65 and in Germany and Japan, this percentage was even higher (>20%). As we mentioned earlier, life span over 80 years before twentieth century was extremely uncommon. Therefore, all disease related advanced age were rare as well.

Before World War II, elderly persons constituted an average of 3–5% of the population. Syphilitic dementia widespread all over the world until it was almost completely eradicated (when penicillin was discovered) after the war. We know that it allows increasing the life span expectancy in developed countries remarkably. Between 1913 and 1920, the medical term dementia praecox had been used to suggest the development of senile-type dementia at a younger age and this terminology also referred to patients with schizophrenia (including paranoia and decreased cognitive capacity) which could be expected to affect any elderly person [27].

In 1920, the uses of *dementia* for what is now understood as schizophrenia and senile dementia helped limit the word's meaning to "permanent, irreversible mental deterioration." This began the change to the more recognizable use of the term today.

Prior to India's independence from Britain in 1947, only 25 medical schools existed in the entire country where concepts about dementia were taught. In 1951, physicians across the field of neurology and neurosurgery united to create the Neurological Society of India (NSI).

Four decades later in 1991, neurologists branched out to establish a separate organization called the Indian Academy of Neurology (IAN) where a lot of research on dementia was done. With the transition to modern medicine that occurred more recently through formal training at medical schools beginning in the 1930s, some criteria about different presentations on dementia changed. The future of neurology in India continues growing rapidly and currently, there are 1100 practicing neurologists attending patients with cognitive decline and dementia and more than 150 post-graduate trainees who join the ranks every year [16].

In 1970s, dementia was delineated from normal aging, and the present concept of dementia was established in Japan [19].

In 1970s, the concept of vascular dementia (VaD) is finally separated and internationally accepted from the purely neurodegenerative form of AD. Many efforts have been released in order to distinguish these entities from the clinical, neuropsychological and pathological point of view for find out a homogenous group of patients who share a common specific underlying mechanism of cognitive decline [28]. The link between senile dementia and Alzheimer's disease was published by Katzmann in 1976 [29]. He described the prevalence and malignancy of AD as a major killer in peoples older than 65 years based on identical pathological findings in both processes. He established non-pathological difference between senile dementia (older than 65) and AD occurring before 65 years old, and the treatment for both entities should be the same. He also considered "senile dementia" as part of aging and not a proper disease. Katzmann documented that AD is a common disease and the fourth or fifth leading cause of death. Thanks to Katzman's criteria, dementia was not considered a part of the normal healthy aging process anymore but the debate between "senile dementia of the Alzheimer's type (over 65 years old) and Alzheimer's disease in younger peoples with the same pathology continue. It was agreed that the age limit was not certain, and the term AD should be reserved for those patients presenting the classical clinical manifestation and the brain pathology described regardless of the age of the patient.

Based on the evidence that many supercentenarians (more than 110 years old) have not dementia, these authors concluded that there was no age at which all persons develop AD, although the incidence of AD increases with age. Nevertheless, dementia is more frequent at the ages of 80 and 84 but peoples reaching the oldest stages have lower chance of developing it and women are more affected than men probably because women have longer lifespan than men [24].

Finally, psychiatry conditions like schizophrenia were removed from the organic brain syndrome group in 1952 and it was not considered as a cause of dementia anymore. On the other hand, the rational cause of senile dementia such as: hardening of the arteries became a main etiology for vascular dementias (VD) when presenting small strokes and now it is named: multi-infarct dementia.

In the 1960s, the seminal neuropathological and clinical studies of the New Castle school in England inaugurated the modern era of vascular dementia [24]. The general concern about AD increased gradually after 1994 when the US president Ronald Reagan disclosure he had been diagnosed with AD.

The term dementia with Lewis Body and the clinical criteria were first introduced and proposed by Mc Keith and colleagues in 1996 during the First International Workshop of the Consortium on Dementia with Lewy Bodies [30].

In the twenty-first century, many types of dementia have been identified being AD and VaD, the commonest one. Fortunately, from the last century, cognitive disorders such as idiopathic normal pressure hydrocephalus have specific treatment, and patients can reach a complete recovery.

Currently, apart for the advance role on the therapeutic field in almost all types of dementias, we highlighted the tremendous progress got in the field of diagnosis mainly in the field of pathological examination and metabolic activity in nuclear medical imaging tests such as single photon emission computed tomography and Positron Emission Tomography scans of the brain.

3. Brief comment about our chapters

In the second chapter of this project, we delivered our personal experience on the most common cognitive disorders and discuss the novel information available in the medical literature on some types of dementia. We described Alzheimer Disease as a progressive non-reversible neurodegenerative disorder, characterized by cognitive decline including learning capacity, emotional and behavioral alterations, motor skills impairment, including dysfunction of the autonomic nervous system and desynchronization of circadian rhythms. It has been predicted that a novel therapeutic agent that delays disease onset and progression by just 1 year would result in 9 million fewer cases by 2050 [31].

Vascular dementia (VaD) can be caused by disturbance of the blood supply to the brain leading to deprivation of the necessary such as nutrients including glucose, amino acids and oxygen to the neurons and its supporting cells. This particular type of dementia is strongly related with multifocal strokes, hypertension and diabetes mellitus type II and it is characterized by mental slowness; impaired initiative, planning, and executive function impairment; personality changes; and gait disorders. Arteriosclerotic brain disease presents as multiple focal areas of hypoperfusion randomly distributed in the cortex, also compromising subcortical structures. This particular pattern is never been observed in A.D. A familial form of VaD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is associated with vascular migraine headache and a subcortical ischemic lesion. CADASIL is caused by a mutation in the NOTCH3 gene on chromosome 19 being the most common genetic form of VaD. The disease is autosomal dominant. Dementia with Lewis Body is a type of dementia associated with abnormal protein deposits (α -synuclein) called Lewy bodies in the central nervous system (CNS), and these abnormal depositions affect the normal activities of the brain leading to clinical features of fluctuating consciousness, behavioral disorders, visual hallucinations, and parkinsonism. The metabolic defects described in this disease are very close to those found in AD, but there is also hypoperfusion in the occipital lobes. Parkinson dementia is characterized by bradykinesia, tremor at rest, gait disturbance, postural problems, rigidity, dysarthria, dysfunction of the judgment,

reasoning, memory, depression, anxiety, insomnia, and cognitive decline due to loss of mid-brain dopaminergic neurons in the pars compacta of the substantia nigra and consequent loss of dopamine input to the caudate nucleus and putamen (striatum), and is more prevalent in men. Idiopathic Parkinson disease with dementia can show hypoperfusion patterns similar to those observed in AD, but basal ganglia hypoperfusion is far more frequent, as is frontal precentral hypoperfusion [32].

Dementia is also part of the clinical manifestation of some types of Parkinsonism such cortico-basal degeneration in which bilateral and symmetrical hypoperfusion of the frontal, parietal lobe and basal ganglia are present. There is symmetrical severe basal ganglia hypoperfusion also affecting the mesial regions of the frontal lobes in supranuclear palsy. The hallmark finding in multiple system atrophy is cerebellar hypoperfusion, besides symmetric basal ganglia hypoperfusion [33].

Mixed Dementia: the association of AD and vascular dementia is the commonest cause of mixed dementia. Idiopathic normal pressure hydrocephalus is characterized by late onset, surgically treated progressive neurodegenerative disease caused by inadequate cerebrospinal fluid (CSF) dynamics and ventriculomegaly while other types including low pressure hydrocephalus are usually secondary to head injury, subarachnoid hemorrhage, infections, and other problems that cause an accumulation of the cerebrospinal fluids (CSF) in the ventricular system of the brain mainly associated to its impaired drainage. Wernicke encephalopathy and Korsakoff syndrome (Wernicke-Korsakoff syndrome) and Alcohol related dementia are preventable, life-threatening neuropsychiatric syndromes resulting from thiamine deficiency mainly in patients with chronic alcoholism, anorexia nervosa or patients that have undergone bariatric surgery for obesity, chronic hepatic disease, immunodeficiency syndromes, nutritional deficiencies of any cause, metastatic carcinomas, hyperthyroidism, prolonged parenteral nutrition, hyperemesis gravidarum, long-term dialysis and diuretic therapy among other causes and clinically, patients' complaints about short-term memory, confusional states, and neuropsychiatry manifestations, HIV-associated neurocognitive disorders (HAND). Many of the complications secondary to HIV-1 infection (including all opportunistic infections) have decreased dramatically excepting HAND which is quite common CNS disorder caused by HIV infection. Huntington disease: in our series of patients presenting Huntington's disease (HD), an important number of them do not have extrapyramidal signs of chorea. Frontotemporal dementia: patients with the different diseases in this group present severe bilateral hypoperfusion in the frontal lobes, predominantly in the mesial structures [34].

We comment about Creutzfeldt Jacob Disease as an extremely uncommon degenerative disorder due to a slow virus (prion) infection that affects the brain and it is also known as mad cow disease. The diagnosis of CJD is usually made when patient older than 60-year-old died and the spongiform changes in the brain post-mortem examination are confirmed. We also discussed about the available update information on the commonest cognitive screening test used to evaluate cognition, and finally we documented our conclusion from previous investigations done.

In the chapter titled "Identification of cognitive impairment markers (Neurospecific proteins, Magnetic Resonance Image) in patients with Diabetes Mellitus type 1," the authors studied

the effects of metabolic disorders on the development of cognitive disorders in patients presenting the abovementioned disorder. They concluded that chronic hyperglycemia and glucose variability are risk factors for the development of cognitive dysfunction, which confirm the need for more severe compensation of the disease. They also highlighted: “For type 1 diabetic patients with unsatisfactory compensation of carbohydrate metabolism the neurophysiological tests looking for cognitive decline should be done.”

In the chapter: Dementia Friendly Assistive Brotherhood Communities, authors from Bournemouth University in United Kingdom highlighted the usability of an assistive software application developed for 8 patients living with dementia (PWLD) and 40 volunteers at 5 different cities of Pakistan.

Overall, the PWLD showed great interest in all the functionalities of the assistive brotherhood community application and were keen to adopt it permanently in their daily life activities. The PWLD specifically appreciated the increased socialization opportunities through the use of assistive brotherhood community application. The implementation of assistive brotherhood community application in the lives of the PWD will increase their confidence, self-esteem, and independence.

Another important chapter on Re-framing and Re-thinking Dementia in the Correctional Setting is written by two authors from University of Adelaide and University of South Australia. They raise the concern about the aging population in the Australian correctional setting. They highlighted the increasingly complex healthcare needs in the prisoner population who present with poorer physical, social, and mental health than the general population, and they also concluded that healthcare services within the correctional environment needs to match that in the general community and this requires the development of policies to support staff to put processes in place that will improve health outcomes for prisoners.

One chapter written by two Korean colleagues from Korea Institute of Science and Technology cover the most relevant aspects of Tau in Tauopathies that leads to Cognitive Disorders and in Cancer. They refer Tau as a copious microtubule-associated protein mainly expressed in neurons; it is also expressed in non-neuronal cell. Tauopathies are neurodegenerative diseases occurring mostly within the neuronal and glial cells of the central nervous system with a conspicuous tau pathology. Tau might have significant functions in non-neuronal cells. In this chapter, authors describe the associations between tauopathies and cancer.

Nowadays, some drugs used for the treatment of cancer are also used for the treatment of different neurological disorders like Parkinson’s disease and AD. They said that Nilotinib is an FDA-approved protein tyrosine kinase inhibitor (TKI)—used for the treatment of chronic myeloid leukemia but it also targets AD and produces neuroinflammation and misfolded proteins that ultimately reduce cognitive damage. In Parkinson’s disease, nilotinib triggers autophagy to remove hyperphosphorylated tau from the brain before they accumulate as plaques.

The hypothalamus plays a central role in autonomic functions, including the generation and control of the circadian rhythms, the thermoregulation, the homeostasis of proteins, the maintenance of energy supply and the feeding behavior. Five authors from Aristotelian University,

Department of Neurology, Laboratory of Neuropathology and Electron Microscopy in Greece afforded this topic (The hypothalamus) and the AD and made a Golgi and electron microscopic study.

They found that the pathological alterations of hypothalamic nuclei in AD would induce the autonomic instability, which would be particularly prominent at the advanced stages of the disease, aggravating the clinical condition of the patients exceedingly, a fact which is also observed in experimental models of AD as well as in the behavioral variant of frontotemporal dementia.

Finally, they concluded that a serious autonomic dysfunction in advanced stages of AD compose the tragic epilogue of the disorder which is related with the involvement of the hypothalamus during the continuous pathological process of the disease.

Other authors from New Zealand made a study about “Effective Restoration Home Support for Older Peoples Living with Dementia and their Caregivers.” One of the most relevant aspects of this investigation was the identification of 10 key factors supporting the adequate restorative home support services for those patients. Its grouped in three primary headings that are congruent with the information published in the medical literature, and they have international implications which include policy and practice that keep the needs and well-being of the dementia diagnosed person and their caregiver central to all decision-making and keeping track of their progression. They also agreed that local solution will influence future decision-making, and this is one of the most important aspects that this chapter highlighted.

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